Neurotransmitter Alterations in PTSD: Catecholamines and Serotonin

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In this chapter we review trauma-related studies involving epinephrine (E), norepinephrine (NE), and serotonin (5-HT). Central catecholamine neurons seem to play a critical role in level of alertness, vigilance, orienting, selective attention, memory, fear conditioning, and cardiovascular responses to life-threatening stimuli. Evidence of catecholamine dysregulation in post-traumatic stress disorder (PTSD) includes exaggerated increases in heart rate and blood pressure when exposed to visual and auditory reminders of trauma, elevated 24-hour urine catecholamine excretion, decreased platelet alpha-2 adrenergic receptor number, exaggerated behavioral, cardiovascular, and biochemical responses to IY yohimbine, decreased cortical brain metabolism secondary to IV yohimbine, and clinical efficacy of adrenergic blocking agents. Serotonin seems to play numerous roles in the central nervous system, including regulation of sleep, aggression, appetite, cardiovascular and respiratory activity, motor output, anxiety, mood, neuroendocrine secretion, and analgesia. Evidence of serotonergic dysregulation in PTSD includes frequent symptoms of aggression, impulsivity, depression and suicidality, decreased platelet paroxetine binding, blunted prolactin response to fenfluramine, exaggerated reactivity to m-chloro-phenyl-piperazine, and clinical efficacy of serotonin reuptake inhibitors. It has been suggested that alterations in NE, E, and 5-HT may have relevance for symptoms commonly seen in survivors with PTSD, including hypervigilance, exaggerated startle, irritability, impulsivity, aggression, intrusive memories, depressed mood, and suicidality.

In recent years there has been a dramatic increase in research related to neurotransmitter alterations in patients with post-traumatic stress disorder (PTSD). These studies in humans have grown out of an extensive animal literature on the neurobiological effects of acute and chronic stress. In this review we will focus on human studies of PTSD that involve catecholamines and serotonin. These systems have been chosen because they are central to the stress response and because, with the exception of hypothalamic-pituitary-adrenal (HPA) and thyroid axes, they have been the primary focus of most studies in PTSD. Alterations in the HPA axis will be covered separately.

Multiple neurobiological systems become activated when animals and humans are threatened by dangerous stimuli. Complex interactions between brain regions and neurochemical systems involved in the processing and responding to meaningful stimuli allow the organism to react in a coordinated and adaptive manner that increases its chances for survival.[1,2] In this chapter we briefly review trauma-related studies involving epinephrine (E), norepinephrine (NE), and serotonin (5-HT). It is important to emphasize that these neurotransmitters do not function in isolation but rather within a remarkably intricate network of regional modulatory systems.

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1084-3612/99/0404-0002$10.00/0

Catecholamines

Preclinical Studies

The locus coeruleus (LC) contains the majority of noradrenergic cell bodies in the brain. It receives diverse afferent input allowing it to process relevant sensory information and has an efferent network that can potentially facilitate anxiety and fear-related skeletal motor, cardiovascular, neuroendocrine, and cognitive responses. Pharmacological or electrical stimulation of the LC elicits fear-related behaviors (in primates) whereas bilateral lesions of the LC dramatically reduce fear behaviors in threatening situations.[3]

A large body of evidence suggests that central noradrenergic nuclei play a critical role in level of alertness, vigilance, orienting, selective attention, memory, and cardiovascular responses to life-threatening stimuli.[4] For example, in rats, cats, and monkeys, alertness is associated with increased LC firing rate, whereas drowsiness is associated with decreased rate of firing. LC activation seems to be particularly responsive to strong stimuli that interrupt ongoing vegetative behaviors such as eating. These stimuli cause a rapid increase in LC firing and a reorienting of the organism's attention. NE also has been shown to enhance strong excitatory or inhibitory input (signal) relative to basal activity (noise) in the same neuron, thus facilitating responsivity to potentially relevant stimuli.[4]

Animal studies strongly suggest that enhanced memory for emotionally arousing, stressful, and averse events is mediated, in part, by catecholamines.[5] Post-training injection of E at moderate doses enhances memory for a variety of learning tasks in rats. A number of animal studies suggest that E, which does not readily

cross the blood brain barrier, ultimately exerts its effects on memory storage through release of central NE and subsequent receptor activation in the amygdala. Increased central NE and glucose may represent common pathways through which a number of other neuromodulators influence memory.[5,6]

Related data suggest that NE, which is released during threatening situations, plays a role in fear conditioning to explicit and contextual stimuli as well as modulation of the acoustic startle response. Fear conditioning refers to the pairing of a fear-provoking aversive event (unconditioned stimulus or US) with an explicit neutral stimulus (conditioned stimulus or CS) that then serves as a specific reminder of the trauma or aversive event. Conditioning can also occur to contextual cues that were present when the CS and US are paired.[7,8]

Numerous studies have revealed alterations in the acoustic startle response (ASR) following pharmacological manipulations of NE transmission. The ASR is a ubiquitous, cross-species response to intense exteroceptive auditory stimuli with abrupt onset.[7] In general, increases in NE are associated with enhanced startle, whereas decreases in NE are associated with depressed startle. For example, the NE agonist amphetamine and the alpha-2 receptor antagonist yohimbine reliably increase ASR in rats, administration of clonidine diminishes ASR.[9]

In addition to its CNS effects on arousal, vigilance, and startle, NE serves as the primary neurotransmitter for postganglionic axons in the peripheral sympathetic nervous system.[10] As part of the fight-flight response, NE facilitates movement of blood from splanchnic and renal regions to skeletal muscles, accelerates heart rate, increases blood pressure, dilates pupils, and constricts skin vasculature. It has been suggested that the paragigantocellularis, a major midbrain noradrenergic nucleus, may activate the peripheral sympathetic nervous system and the LC in parallel and thus play an important role in coordinating their activity during arousing and stressful situations.[4]

Numerous preclinical studies have shown that animals exposed to repeated stressors often react to future stressors with exaggerated behavioral, physiological, and biochemical responses (stress sensitization). It has been suggested that chronic stress-induced increases in NE release are related to increased synthesis of NE as reflected by elevated levels of tyrosine hydroxylase, dopamine B hydroxylase, and NE found in the brains, sympathetic nerve terminals, and adrenal glands of repeatedly stressed animals.[11,12] Other factors, such as corticotropin releasing factor and neuropeptide Y, which affect firing rate of the LC and/or modulation of presynaptic NE release and postsynaptic responsiveness to NE, also have been implicated in enhanced noradrenergic function in chronically stressed animals.[13,14]

Clinical Studies

Psychophysiology. Since the 1940s, when Kardiner observed that combat veterans with "physioneurosis" were exquisitely reactive to sensory stimuli associated with their combat experiences, researchers have conducted a large number of psychophysiological studies in survivors of overwhelming psychological trauma. These studies typically measure biological parameters such as blood pressure, heart rate, skin conductance, and electromyographic (EMG) activity of facial muscles at baseline and in response to various trauma-related and generic stressors. Most studies of baseline physiological arousal have reported no differences between PTSD and control groups. The studies that have found elevations in baseline heart rate may be confounded by anticipatory anxiety as subjects await presentation of trauma-related cues.[15]

On the other hand, across all published psychophysiological studies, approximately two thirds of PTSD subjects show exaggerated reactivity to internal or external trauma-associated cues.[15,16] Among those with severe PTSD, the percentage seems to be even higher. Comparison groups with significantly lower recorded reactivity include healthy nontraumatized controls, individuals with anxiety disorders other than PTSD, and traumatized combat veterans without PTSD.

Most studies of ASR in PTSD also have found an increase in magnitude of the startle reflex in subjects with PTSD compared with non-PTSD controls.[17] Additionally, the increase in magnitude of the startle reflex in subjects with PTSD may be exacerbated under conditions of darkness, threat of shock, or treatment with the alpha-2 adrenoceptor antagonist yohimbine.[7,17]

Baseline catecholamines. Impressed by the consistency of psychophysiological findings in trauma survivors with PTSD, researchers began to investigate the biochemical underpinnings of sympathetic nervous system activation in this population. Baseline investigations of catecholamine function have included plasma, 24-hour urine, adrenergic receptor, and second messenger studies.[2]

Baseline studies generally have found no significant differences between plasma NE in subject groups with PTSD compared with healthy controls. A number of these studies are difficult to interpret because veni puncture itself may be painful and serve as a stressor that could affect catecholamine levels. Nevertheless, at least 3 studies involving combat veterans have found similar baseline plasma NE levels in combat veterans with PTSD and healthy controls, and 1 study has reported comparable levels of MHPG. Of note, Yehuda and colleagues sampled plasma NE and MHPG under unstimulated conditions over a 24-hour period and found no differences between PTSD subjects and controls in plasma MHPG but did find significantly higher mean NE levels in combat veterans with PTSD alone

compared with combat veterans with PTSD and comorbid depression, patients with major depressive disorder alone, and healthy controls.[18]

Unlike plasma studies, 24-hour urine investigations of catecholamine excretion generally have found elevated values in subjects with PTSD compared with controls. In combat veterans[2] 3 published reports have found elevated urine values for both NE and E. Kosten et al reported higher urine norepinephrine in combat veteans with PTSD compared with patients with schizophrenia or major depression. In the PTSD group, NE remained elevated throughout several months of hospitalization. Yehuda et al compared combat veterans diagnosed with PTSD with normal controls and found the inpatient veteran group to have significantly higher NE and E. An outpatient veteran group with PTSD had higher levels of NE but not E values. Pitman et al found that combat veterans with and without PTSD had comparable NE values, and that these values were similar to the values reported by Yehuda and colleagues.

Elevated 24-hour urine NE and E values also have been reported in noncombat populations. In a study comparing 19 women with histories of childhood sexual abuse (11 with PTSD and 8 without PTSD) to 9 nonabused controls, Lemieux and Coe[19] reported significantly higher NE and E levels in the PTSD group compared with the nonabused control group. The non-PTSD sexual abuse group did not differ significantly from either the PTSD or the nonabused control group. Similar but nonsignificant patterns were seen for urine dopamine. A significant positive correlation was found between NE and the intrusive subscale of the IES and between E and all 3 subscales of the IES. Sexually abused girls also have been reported as having greater 24-hour excretion of homovanillic acid and having trends toward greater excretion of urinary vanilmandelic acid, metanephrine, and total catecholamines (E, NE, and dopamine) compared with demographically matched healthy controls.[20] In a separate study, children with PTSD excreted significantly more E in their urine than children diagnosed with overanxious disorder or than healthy controls.[21] Finally, 5 years after the Three Mile Island nuclear power station accident, Davidson and Baum[22] found significantly higher NE levels in residents living close to the station compared with residents living 80 miles away, implying that stress levels were higher in residents living closer to the station.

The neurochemical message of NE and E is translated, in part, by alpha-2 adrenergic receptors. Two separate radioligand-binding studies, one involving combat veterans and another involving traumatized children, have reported fewer total alpha-2 adrenergic receptor binding sites per platelet in subjects with PTSD compared with controls. Reduced alpha-2 adrenergic receptor number also has been observed in congestive heart failure and hypertension, conditions characterized by chronic and excessive catecholamine activity. It has been hypothesized that chronic elevation of circulating catecholamines causes a down-regulation or reduced number of available receptor sites that serves an adaptive role in response to overstimulation by agonist.[23] Studies looking at baseline beta-adrenergic receptor-mediated adenylate cyclase levels have been mixed.

Challenge studies: catecholamines. The following studies were designed to evaluate catecholamine activity under controlled conditions that intentionally stimulated the subject with external stimuli such as traumatic scripts or exogenously administered biological substances. Also briefly discussed are several in vitro paradigms using platelets and lymphocytes.

In an attempt to assess dynamic functioning and regulation of alpha-2 adrenergic receptors, Perry[25] incubated intact platelets with high levels of E and found a greater and more rapid loss in receptor number among the PTSD group than controls. These findings suggested that alpha-2 receptors in combat veterans with PTSD were more sensitive to down-regulation. The effects of E on forskolin-stimulated adenylate cyclase activity have been mixed. Probes of the lymphocyte beta-adrenergic receptor mediated cyclic adenosine 3′,5′-monophosphate system in subjects with PTSD also have provided a mixture of results such that no specific hypotheses regarding alterations in this system are supported.[2]

In an in vitro challenge, McFall et al[24] reported parallel increases and higher levels of subjective distress, blood pressure, heart rate, and plasma E in combat veterans with PTSD than in control subjects during and after a combat film but not in response to the film of an automobile accident. These findings suggested that heightened physiological reactivity was related to elevations of circulating E. Using auditory combat-related stimuli, Blanchard et al[25] similarly reported greater increases in heart rate and plasma NE in combat veterans with PTSD compared with combat veterans without PTSD.

Specific pharmacological probes in subjects with PTSD have included challenges with desipramine, lactate, and yohimbine. Using the growth hormone response to desipramine as a probe of postsynaptic alpha-2 adrenergic receptor function, Dinan et al[26] found no differences between 8 traumatized women with PTSD and control subjects in desipramine-stimulated growth hormone levels. Rainey et al and Jenson et al have reported panic attacks and flashbacks in response to IV lactate among veterans and civilians with PTSD. Although the precise mechanism of lactate-induced anxiety and panic is unknown, central noradrenergic stimulation has been implicated.[27]

Yohimbine, an alpha 2-adrenergic receptor antagonist that activates noradrenergic neurons by blocking the alpha-2 adrenergic autoreceptor and thereby increasing presynaptic noradrenergic release, has been studied in combat veterans with PTSD.[28] Responses to intravenous yohimbine were compared between 20

Vietnam combat veterans with PTSD and 18 healthy controls. Although yohimbine acts on multiple neurotransmitter systems, it primarily affected the noradrenergic system at the study dose. Yohimbine induced panic attacks in 70% and flashbacks in 40% of PTSD patients. There were no yohimbine-induced panic attacks or flashbacks among the control group. A greater elevation of plasma MHPG after yohimbine administration suggested abnormal presynaptic noradrenergic reactivity among patients in the PTSD group.

Yohimbine has produced a similar rate of panic attacks in patients with panic disorder but not in patients with major depressive disorder, schizophrenia, obsessive-compulsive disorder, or even generalized anxiety disorder, which suggests that PTSD and panic disorder share a common neurobiological abnormality related to altered sensitivity of the noradrenergic system. Eighty-nine percent of patients meeting criteria for both PTSD and panic disorder had yohimbine-induced panic attacks, suggesting that this subgroup of patients may have an especially pronounced abnormality of the noradrenergic system.

A recent family study[29] investigating 24 PTSD probands who participated in yohimbine challenge studies reported a 2.4% rate of panic disorder in 85 first-degree relatives of probands who had yohimbine-induced panic attacks compared with a 3.2% rate of panic disorder in the 63 relatives of probands who did not have yohimbine-induced panic attacks. The rates of panic disorder in the relatives of comparison healthy probands and comparison panic disorder probands was 0.0% and 15.9%, respectively. Thus the rate of panic disorder in the first-degree relatives of PTSD probands with and without yohimbine-induced panic attacks was similar, suggesting that a family history of panic disorder is not a predisposing vulnerability for the development of yohimbine-induced panic attacks in patients with PTSD. The data also support the possibility that panic symptoms seen in patients with PTSD result from nongenetic factors such as exposure to traumatic events.

A final provocation study involving yohimbine was conducted by Bremner et al,[30] who administered a single bolus of [F-18]2-fluoro-2-deoxyglucose to combat veterans with PTSD (n = 10) and healthy controls (n = 10) that was immediately followed by either IV yohimbine (0.4 mg/kg) or placebo infusion. After completion of the yohimbine or placebo infusion, subjects underwent positron emission tomography (PET) scanning for 60 minutes. The PTSD group had a decrease in metabolism in neocortical areas (orbitofrontal, temporal, prefrontal, and parietal cortex), whereas controls had increased metabolism in these areas. The results are consistent with the notion that PTSD patients as a group released more NE than control subjects because of their greater sensitivity to yohimbine. Increased NE resulted in a relative decrease in brain metabolism, which may be related to the degree of yohimbine-induced anxiety/panic and PTSD-specific symptoms such as impaired attention and hypervigilance.

In summary, baseline or resting studies generally have found little or no differences in plasma catecholamine levels between subjects with PTSD and healthy control subjects. However, most 24-hour urine studies have reported increased excretion of catecholamines, and most challenge studies have found evidence for hypersensitivity of catecholamine systems. Twenty-four-hour urine samples reflect the summation of day-to-day stresses and phasic physiological changes in response to meaningful stimuli, as well as tonic resting levels of autonomic arousal.[31]

The above reviewed studies point to increased responsiveness of the sympathetic nervous system (SNS) that is detectable under conditions of stress in severely traumatized individuals with PTSD. The findings are consistent with behavioral sensitization and fear-conditioning models of PTSD.[2] Furthermore, several recent studies in healthy humans[5] support preclinical findings that memories for aversive events are enhanced by catecholamines. Central beta-adrenergic receptors have been implicated because propranolol, but not nadolol, has been shown to block enhanced encoding and recall for arousing stimuli. These data are consistent with the possibility that stressful and traumatic events stimulate the release of E and NE, and that these neurotransmitters cause an overconsolidation of memory for the stressful event that may later contribute to nightmares and intrusive memories.[32]

Serotonin

Preclinical

(For reviews see references 33 and 34). Efferents from the brainstem raphe nuclei form a large, complex, and expansive network in the brain. It has been hypothesized that 5-HT plays numerous roles in the central nervous system (CNS), including regulation of sleep, aggression, appetite, cardiovascular and respiratory activity, motor output, anxiety, mood, neuroendocrine secretion, and analgesia. A large number of preclinical studies suggest that 5-HT has excitatory effects on alpha motoneurons and an inhibitory effect on primary sensory neurons.

During normal waking states serotonergic neurons discharge in a stable, slow, and regular pattern. As the organism becomes drowsy and enters slow-wave sleep, serotonergic neuronal activity declines until firing stops during rapid eye movement (REM) sleep. Just before a person awakens from REM sleep, serotonergic neuronal firing rate returns to baseline. Firing rates elevated above baseline have been observed during oral-buccal activities such as chewing, licking, and grooming. Of note, serotonergic neuronal firing rate does not increase in response to environmental and physiological stressors such as loud noises or drug induce decreases in

blood pressure. Furthermore, when the organism orients to an arousing stimulus, serotonergic neurons may stop firing for several seconds.

It has been suggested that 5-HT and NE may play complementary roles in the organisms response to arousing stimuli. For example, during the orienting response, NE neuronal firing rate increases dramatically, whereas firing rate of 5-HT neurons decreases or even ceases momentarily. An increase in LC firing rate is associated with an increase in signal-to-noise ratio and a selective focusing of attention. A decrease in 5-HT neuronal firing is associated with disinhibition of sensory processing (normally sensory processing is dampened by 5-HT), a decrease in vegetative activities, and suppression of gross motor movement. Together the actions of NE and 5-HT ensure that the organism will stop ongoing activity to maximally attend to the arousing stimulus of interest.

Research has shown that ASR is sensitive to manipulations of 5-HT.[35] Direct administration of 5-HT into the ventricles depresses ASR, reduction of 5-HT (tryptophan-free diet) enhances ASR. Further, 5-HT releasers (such as fenfluramine) reduce ASR, the 5-HT 1A agonist 8-OH-DPAT increases ASR, and animals without the 5-HT2 receptor show a reduction in ASR.

Prepulse inhibition (PPI) is the reduction in amplitude of the ASR when the startling stimulus is preceded by a detectable but nonstartling stimulus. It is believed to reflect a central mechanism of behavioral inhibition. Changes in PPI may indicate alterations in attentional processing that are symptomatic of PTSD. PPI is affected by alterations in 5-HT activity.[36] For example, PPI is disrupted after treatment with 5-HT releasers, alpha-ethyltryptamine (AET), and 5-HT1A agonists such as buspirone. On the other hand, animals lacking the 5-HT1B receptor show an increase in PPI.

Petty et al[37] and others have shown that acute stress causes increased 5-HT in medial prefrontal cortex, nucleus accumbens, amygdala, and lateral hypothalamus, chronic inescapable stress causes depletion of 5-HT in frontal cortex with accompanying behavioral deficts that have been described as learned helplessness. Pretreatment with benzodiazepines or tricyclic antidepressants can prevent stress-induced decreases in serotonin and accompanying behavioral deficits. Furthermore, administration of 5-HT or 5-HT1A agonists has been shown to reverse stress-induced behavioral deficits.

Clinical Studies

A large body of indirect evidence suggests that 5-HT neuronal activity may be important in the pathophysiology of trauma-related symptomatology. In humans, low sertonin (5-HT) functioning has been associated with aggression, impulsivity, and suicidal behavior.[2] These behaviors are frequently described in patients with PTSD. Serotonin reuptake inhibitors have been shown to be effective in treating the trauma-related symptoms of some patients with PTSD.[38] Vietnam veterans[7] and children[39] with PTSD show a reduction in PPI compared with controls.

To date there have been several reports of baseline serotonergic function in PTSD.[40,41] For example, in one study, platelet paroxetine binding was examined in 20 combat veterans with PTSD under resting conditions. Platelet 5-HT uptake was significantly decreased in PTSD patients compared with normals, and in PTSD patients meeting criteria for comorbid major depressive disorder. The specificity of these findings has yet to be determined because decreased platelet 5-HT uptake also has been reported in patients with depression and alcoholism.

The prolactin response to the serotonin releasing and uptake inhibitor d-fenfloramine[42] and the behavioral effects of m-chloro-phenyl-piperazine (MCPP)[43] also have been examined in combat veterans with PTSD. The hypothalamus receives stimulatory input from 5-HT nerve terminals originating in the dorsal raphe. In response to hypothalamic stimulation the pituitary then secretes prolactin. In 8 subjects with PTSD, Davis et al[42] found that the prolactin response to d-fenfloramine was blunted compared with controls and that symptoms of reexperiencing and aggression were inversely correlated with change in prolactin.

MCPP is a 5-HT agonist with predominant effects on 5-HT2 and 5-HT1c receptors. In a study conducted by Southwick et al,[43] 26 subjects with PTSD and 14 healthy controls each received an infusion of yohimbine hydrochloride, MCPP, or saline solution on 3 separate test days in a randomized balance order and in double-blind fashion. Forty-two percent of patients and 7% of controls experienced a panic attack in response to yohimbine, whereas 31% of patients and no healthy controls had a panic attack after MCPP administration. Flashbacks were induced by yohimbine in 8 patients, by MCPP in 7 patients, and by placebo in 2 patients. There were no flashbacks in the control group under any of the 3 conditions. This study provided preliminary evidence for possible neurobiological subgroups of patients with PTSD with 1 group showing increased reactivity of the noradrenergic system and the other increased reactivity of the serotonergic system. The study also showed that panic attacks and flashbacks can be induced in combat veterans with PTSD by multiple anxiogenic agents that have differing mechanisms of action.

Overall, the above preclinical and clinical studies suggest that traumatic stress can cause chronic alterations in central 5-HT function and that stress-related symptoms and behavior changes may be related to a number of symptoms commonly seen in PTSD.

Conclusion

PTSD seems to be a multisystem neurobiological disorder that involves alterations in numerous stress-related

neurotransmitter systems. We briefly have reviewed trauma-related preclinical and clinical studies involving the norepinephrine and serotonin systems. The degree to which hereditary and developmental factors contribute to noradrenergic and serotonergic responses in situations of acute and chronic stress is not yet known. It has been suggested that alterations in these neurotransmitter systems may have relevance for a number of symptoms commonly seen in survivors with PTSD such as hypervigilance, exaggerated startle, irritability, impulsivity, aggression, intrusive memories, depressed mood, and suicidality. The efficacy of adrenergic blocking agents and serotonin reuptake blockers for the treatment of many of these PTSD symptoms provides further evidence for the clinical relevance of noradrenergic and serotonergic alterations in a substantial number of trauma survivors.

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